IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
Clarksburg

ACTELION PHARMACEUTICALS LTD.,

Plaintiff,

v.

CIVIL ACTION NO. 1:20-CV-110
Judge Bailey

MYLAN PHARMACEUTICALS, INC.,

Defendant.

ORDER

This patent infringement case involves two United States Patents owned by Actelion Pharmaceuticals Ltd. ("Actelion"), U.S. Patent Nos. 8,318,802 (the "'802 patent") and 8,598,227 (the "'227 patent") (collectively, the "patents-in-suit"). [Doc. 1]. The pharmaceutical composition and methods described in these patents are used to produce VELETRI®, a drug indicated for the treatment of pulmonary arterial hypertension. [Id. at 4].

The parties dispute the construction of one claim term: "a pH of 13 or higher." For the reasons that follow, this Court adopts in part Mylan's proposed construction of this term.

I. Background[1] and Procedural History

In this first-filed Hatch-Waxman suit, Actelion alleges that the defendant, Mylan Pharmaceuticals Inc. ("Mylan"), has infringed the patents-in-suit. [Doc. 1 at 5–7]. Actelion

[1] The United States Court of Appeals for the Federal Circuit does not appear to take issue with Judge Keeley's background of the case. Thus, this Court adopts (and plagiarizes) in full this section from Judge Keeley's February 14, 2022 Order.

holds approved New Drug Application No. 022260, under which the United States Food and Drug Administration ("FDA") granted approval on June 27, 2008 for epoprostenol sodium for injection, eq. 1.5 mg/vial, and on June 28, 2012 for epoprostenol sodium for injection, eq. 0.5 mg/vial, both marketed in the United States under the trade name VELETRI®. [Id. at 4]. The patents-in-suit are listed in the FDA's Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, for VELETRI®. [Id.]. After receiving notice and certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that Mylan had filed Abbreviated New Drug Application No. 213913, seeking FDA approval to manufacture and sell generic epoprostenol sodium for injection, 1.5 mg/vial and 0.5 mg/vial, Actelion sued Mylan for infringement. [Id. at 5].

After the parties had briefed their respective positions as to how the Court should construe the disputed claim term in the patents-in-suit, the Court held a ***Markman*** hearing on August 11, 2021. [Doc. 95].

Judge Keeley issued her February 14, 2022 Order, adopting Actelion's proposed construction and construing "a pH of 13 or higher" with "its plain and ordinary meaning, that is, a pH of 13, or a pH higher than 13." [Doc. 143 at 23]. More specifically, "[a]fter considering the claims, the entirety of the specifications of the patents-in-suit, and the prosecution history of the '802 patent," Judge Keeley found that "[n]othing in the file history indicates that Actelion intended to use a more exacting level of measurement or to forfeit the use of ordinary rounding rules." [Id. at 22–23].

Following entry of Final Judgment and Order of Permanent Injunction Based on Stipulation of Parties [Doc. 185], Mylan Pharmaceuticals Inc. ("Mylan") appealed.

On November 6, 2023, the United States Court of Appeals for the Federal Circuit vacated this Court's claim construction order [Doc. 143] with respect to the term "a pH of 13 or higher" and the judgment of infringement, and remanded for this Court to consider the extrinsic evidence and its impact on claim construction. *See* [Doc. 191]. The Mandate from the Federal Circuit issued on December 13, 2023. *See* [Doc. 206].

Following remand, this Court directed the parties to file briefing on extrinsic evidence only and its impact on claim construction. *See* [Doc. 193]. The parties filed their respective briefing on November 21, 2023. *See* [Docs. 197 & 198].

II. Legal Standards

The construction of patent claims is a matter of law governed by federal statutes and the decisions of the Supreme Court of the United States and the United States Court of Appeals for the Federal Circuit. *See* ***Markman v. Westview Instruments, Inc.***, 52 F.3d 967, 979 (Fed. Cir. 1995). When interpreting the meaning of a claim, a court may consider the context, the specification, and the prosecution histories as intrinsic evidence. ***Id***. (quoting ***Unique Concepts, Inc. v. Brown***, 969 F.2d 1558, 1561 (Fed. Cir. 1991)). "It is a bedrock principle of patent law that claims of a patent define the invention to which the patentee is entitled the right to exclude." ***Phillips v. AWH Corp.***, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation marks omitted). The description of an invention in the claims, therefore, limits the scope of the invention. ***Id***. "[T]here is no magic formula or catechism for conducting claim construction." ***Id***. at 1324. Instead, the Court is free to attach the appropriate weight to appropriate sources "in light of the statutes and policies that inform patent law." ***Id***.

"[T]he words of a claim are generally given their ordinary and customary meaning [which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." ***Id.*** at 1312–13 (internal citations and quotation marks omitted). "[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent." ***Id.*** at 1321 (citing ***Medrad, Inc. v. MRI Devices Corp.***, 401 F.3d 1313, 1319 (Fed. Cir. 2005) ("We cannot look at the ordinary meaning of the term . . . in a vacuum. Rather, we must look at the ordinary meaning in the context of the written description and the prosecution history.")).

When construing patent claims, then, a court must consider the context of the entire patent, including both asserted and unasserted claims. ***Id.*** at 1314. Because a patent will ordinarily use patent terms consistently, "the usage of a term in one claim can often illuminate the meaning of the same term in other claims." ***Id.*** Accordingly, "[d]ifferences among claims" can provide insight into "understanding the meaning of particular claim terms," and "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." ***Id.*** at 1314–15 (citing ***Liebel-Flarsheim Co. v. Medrad, Inc.***, 358 F.3d 898, 970 (Fed. Cir. 2004)).

Pursuant to 35 U.S.C. § 112(a), an inventor must use the patent specification to describe the claimed invention in "full, clear, concise, and exact terms." The patent specification therefore "is always highly relevant to the claim construction analysis.

Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." ***Vitronics Corp. v. Conceptronic, Inc.***, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

"[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." ***Phillips***, 415 F.3d at 1316. "Even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." ***Hill-Rom Servs., Inc. v. Stryker Corp.***, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (quoting ***Liebel-Flarsheim***, 358 F.3d at 906) (internal quotation marks omitted).

Nevertheless, a court may not import a limitation into the claims from the specification. ***Phillips***, 415 F.3d at 1323. The Federal Circuit has "repeatedly warned" against limiting the claims to the embodiments specifically described in the specification. ***Id.*** In other words, a court should not construe the patent claims as being limited to a single embodiment simply because the patent describes only one embodiment. ***Id.*** (citing ***Gemstar-TV Guide Int'l Inc. v. Int'l Trade Comm'n***, 383 F.3d 1352, 1366 (Fed. Cir. 2004)).

A court "should also consider the patent's prosecution history, if it is in evidence." ***Markman***, 52 F.3d at 980. The prosecution history, which is "intrinsic evidence," "consists of the complete record of the proceedings before the PTO [Patent and Trademark Office] and includes the prior art cited during the examination of the patent." ***Phillips***, 415 F.3d at 1317. "[T]he prosecution history can often inform the meaning of the claim language by

demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." ***Id.***

"The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correction construction." ***Renishaw PLC v. Marposs Societa' per Azionio***, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." ***Osram GmbH v. Int'l Trade Comm'n***, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (quoting ***Modine Mfg. Co. v. U.S. Int'l Trade Comm'n***, 75 F.3d 1545, 1550 (Fed. Cir. 1996)).

A court thus begins its analysis by looking to the "actual words of the claim," ***Becton, Dickinson and Co. v. Tyco Healthcare Group, LP***, 616 F.3d 1249, 1254 (Fed. Cir. 2010), as well as the context in which the disputed term appears. ***Phillips***, 415 F.3d at 1314. Patent claims come in two general forms, independent and dependent. 35 U.S.C. § 112(c). Independent claims do not refer to another claim of the patent and are read separately to determine their scope. ***Inamin, Ltd. v. Magnetar Tech. Corp.***, 623 F.Supp.2d 1055, 1065 (C.D. Cal. 2009). Dependent claims, by contrast, refer to at least one other claim, include all of the limitations of the claim to which they refer, and specify a further limitation on that claim. 35 U.S.C. § 112(d); *see also* ***Monsanto Co. v. Syngenta Seeds, Inc.***, 503 F.3d 1352, 1357 (Fed. Cir. 2007).

In most cases, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term. In such circumstances, it is improper to rely on extrinsic

evidence. *See, e.g.*, ***Pall Corp. v. Micron Separations, Inc.***, 66 F.3d 1211, 1216 (Fed. Cir. 1995) ("In construing the claims we look to the language of the claims, the specification, and the prosecution history. Extrinsic evidence may also be considered, *if needed* to assist in determining the meaning or scope of technical terms in the claims.") (citations omitted, emphasis added); ***Hormone Research Foundation, Inc. v. Genentech, Inc.***, 904 F.2d 1558, 1562 (Fed. Cir. 1990) ("Claim interpretation involves a review of the specification, the prosecution history, the claims (including unasserted as well as asserted claims), and, *if necessary*, other extrinsic evidence, such as expert testimony.") (citations omitted, emphasis added).

Although the Federal Circuit has emphasized the importance of intrinsic evidence, the Federal Circuit has also "authorized district courts to rely on extrinsic evidence, which 'consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises.'" ***Phillips***, 415 F.3d at 1317 (quoting ***Markman***, 52 F.3d at 980 (citing ***Seymour v. Osborne***, 78 U.S. 516, 546 (1870))). "Extrinsic evidence is that evidence which is external to the patent and file history, such as expert testimony, inventor testimony, dictionaries, and technical treatises and articles." ***Vitronics Corp.***, 90 F.3d at 1584 (citing ***Markman***, 52 F.3d at 979). However, "extrinsic evidence in general . . . may be used only to help the court come to the proper understanding of the claims; it may not be used to vary or contradict the claim language. . . . Nor may it contradict the import of other parts of the specification." ***Id***. (citing ***Markman***, 52 F.3d at 981).

With these legal principles in mind, the Court turns to the construction of the disputed term in the asserted claims of the patents-in-suit.

III. Patents-In-Suit

A. The Claims

1. The '802 Patent

Independent claim 1 of the '802 patent reads:

> A lyophilized pharmaceutical composition comprising:
> (a) a unit dose of 0.5 mg or 1/5 mg of epoprostenol or a salt thereof;
> (b) arginine; and
> (c) sodium hydroxide,
> wherein said lyophilized pharmaceutical composition is
> (I) formed from a bulk solution having a pH of 13 or higher and (ii) capable of being reconstituted for intravenous administration with an intravenous fluid.

[Doc. 63-4 at 18:45–54].

Independent claim 11 reads:

> A lyophilisate formed from a bulk solution comprising:
> (a) epropostenol or a salt thereof;
> (b) arginine;
> (c) sodium hydroxide; and
> (d) water,
> wherein the bulk solution has a pH of 13 or higher, and wherein said lyophilisate is capable of being reconstituted for intravenous administration with an intravenous fluid.

[Id. at 19:13–20].

2. The '227 Patent

Independent claim 16 reads:

> A method for treating a patient suffering from a disease selected from the group consisting of cardiovascular disease, atherosclerosis, arteriosclerosis, congestive heart failure, angina pectoris, and hypertension, said method

> comprising the steps of (1) combining an intravenous fluid with an effective amount of a lyophilized pharmaceutical composition comprising:
> (a) a unit dose of 0.5 mg or 1.5 mg of epoprostenol or a salt thereof;
> (b) arginine; and
> (c) sodium hydroxide,
> wherein said lyophilized pharmaceutical composition is formed from a bulk solution having a pH of 13 or higher; and (2) administering the resulting intravenous fluid of step (1) to a patient in need thereof.

[Doc. 63-5 at 19:40–45].

Independent claim 22 reads:

> A method for treating a patient suffering from a disease selected from the group consisting of cardiovascular disease or disorder, atherosclerosis, arteriosclerosis, congestive heart failure, angina pectoris, and hypertension, said method comprising the steps of (1) combining an intravenous fluid with an effective amount of a lyophilized pharmaceutical composition comprising:
> (a) a unit dose of 0.5 mg or 1.5 mg of epoprostenol or a salt thereof;
> (b) 50 mg of arginine;
> (c) Mannitol or sucrose; and
> (d) sodium hydroxide.
> wherein said lyophilized pharmaceutical composition is formed from a bulk solution having a pH of 13 or higher; and [sic] (2) [sic] and (2) administering the resulting intravenous fluid of step (1) to a patient in need thereof.

[Id. at 20:3–19].

Independent claim 32 states:

> A method for treating a patient suffering from a disease selected from the group consisting of cardiovascular disease, atherosclerosis, arteriosclerosis, congestive heart failure, angina pectoris, and hypertension, said method comprising the steps of (1)(I) reconstituting an
> effective amount of a lyophilized pharmaceutical composition comprising:
> (a) a unit dose of 0.5 mg or 1.5 mg of epoprostenol or a salt thereof;
> (b) 50 mg of arginine;
> (c) Mannitol or sucrose; and
> (d) sodium hydroxide,
> in 5 mL [sic] of water for injection or 0.9% sodium chloride solution to form a reconstituted solution, wherein said lyophilized pharmaceutical composition is formed from a bulk solution having a pH of 13 or higher, (1)(ii) diluting the reconstituted solution of step (1)(I) with a second diluent to form a diluted solution; and (2) administering the resulting diluted solution of step (1)(ii) to a patient in need thereof.

[Id. at 20:43–30].

Finally, independent claim 40 states:

A method for treating a patient suffering from a disease selected from the group consisting of cardiovascular disease, atherosclerosis, arteriosclerosis, congestive heart failure, angina pectoris, and hypertension, said method comprising the steps of (1)(I) reconstituting an effective amount of a lyophilized pharmaceutical composition comprising:
(a) a unit dose of 0.5 mg or 1.5 mg of epoprostenol or a salt thereof;
(b) 50 mg of arginine;
(c) Mannitol or sucrose; and
(d) sodium hydroxide,
in 5 mL [sic] of water for injection to form a reconstituted solution, wherein said lyophilized
pharmaceutical composition is formed from a bulk solution having a pH of 13 or higher; (1)(ii) diluting the reconstituted solution of step (1)(I) with water for injection to form a diluted solution; and (2) administering the resulting diluted solution of step (1)(ii) to a patient in need thereof.

[Id. at 21:10–27].

B. The Specification

The specification in the '802 patent provides in pertinent part:

The present inventor has unexpectedly found that poprostenol solution in the presence of an alkalinizing agent, and high pH (>11) is very stable compared to Flolan. Accordingly, one object of the present invention is to provide pharmaceutical compositions containing epoprostenol or a salt thereof, and at least one alkalizing agent at pH>11. The composition is characterized by improved stability upon reconstitution with commercially available intravenous (IV) fluids.

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The composition is preferably a lyophile produced by freeze drying (lyophilizing) a bulk solution containing epoprostenol, or a salt thereof, and arginine. The pH of the bulk solution is preferably adjusted to about 12.5-13.5, most preferably 13, by the addition of sodium hydroxide.

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The pH of the bulk solution is adjusted to >11 with sodium hydroxide prior to lyophilization. In another embodiment, the composition of the present

> composition contains epoprostenol (or a salt thereof, such as epoprostenol sodium), and arginine. The composition may also include a base. . . . The base is added so that the pH of the bulk solution is greater than 11, preferably greater than 12, and most preferably 13 or higher.
>
> ***
>
> In another embodiment . . . [t]he pH of the bulk solution is adjusted to 13.0 with the base.
>
> ***
>
> In the next stage of development, we screened several lyophilized formulations with the pH of bulk solution for lyophilization adjusted between 10.5 and 13 in the presence of different excipients. . . . As shown in the Table 8 above, the stability of epoprostenol is better at pH 13 compared to lower pH samples.
>
> ***
>
> As seen from the data above, epoprostenol is most stable in mannitol/arginine containing formulations when the pH of the bulk solution [is] adjusted to 13.

[Doc. 63-4 at 4:8–15; 5:29–43; 6:63–7:5; 7:6–17; 10:62–11:55; 14:26–28].

C. Patent Prosecution History

Although the prosecution history of the '277 patent is not in evidence, the file history of the '802 patent is instructive because those two patents share a specification. *See* ***Capital Mach. Co. v. Miller Veneers, Inc.***, 524 F.App'x 644, 649 (Fed. Cir. 2013) ("We have held that the prosecution history regarding a claim term is pertinent when interpreting the same term in both later-issued and earlier-issued patents in the same family.") Pursuant to 35 U.S.C. §§ 112, 102, and 103, the Examiner initially rejected several claims of the '802 patent because the phrase, "wherein the composition is reconstituted, the pH of the reconstituted solution is greater than 11," lacked clarity and was indistinguishable

from the prior art [Doc. 62-4]. In response, Actelion amended the claims so that the pH of the solution was "greater than 12," but the Examiner was still unpersuaded.

The claims eventually were allowed once Actelion amended the claims at issue to include the term "a pH of 13 or higher." According to the Examiner:

> Applicant has demonstrated unexpected results with respect to compositions made with solutions of pH 13 or higher as shown in tables 8 and 9 of the specification (example 4, paragraphs [0057-0058]). The stability of the composition is greatly increased when reconstituted versus compositions with a pH of 12 or lower. This is an unexpected result as the prior art does not teach pH of 13 as having advantages over pH 11 or 12.

[Id.].

IV. Discussion

The central conflict identified by the Federal Circuit for this Court to address is "what the significant digits are for 'a pH of 13.'" [Doc. 191 at 2]. The Federal Circuit agreed with Judge Keeley that the specification uses various degrees of precision, noting: "the specification uses both '13' and '13.0'—and various degrees of precision for pH values generally—throughout." [Doc. 191 at 10]. However, the Federal Circuit found that this rendered the intrinsic record "rather equivocal" and found that "the extrinsic evidence relied on by the parties—but unconsidered by the district court . . . highly relevant to how a person of ordinary skill would understand the language of 'a pH of 13.'" [Id. at 7].

A. Intrinsic Evidence

1. Claim Language

This Court first starts with the claim language. *See* ***Sunovion Pharms., Inc. v. Teva Pharms., USA, Inc.***, 731 F.3d 1271, 1276 (Fed. Cir. 2013) (explaining that we first, and primarily, rely on intrinsic evidence like the claims themselves when construing claim terms); *see also* ***Prima Tek II, L.L.C. v. Polypap, S.A.R.L.***, 318 F.3d 1143, 1148 (Fed. Cir. 2003) ("Claim construction begins with the words of the claim."). The claim language, "a pH of 13 or higher," is a range with a specified lower limit. On appeal, Mylan argued that "the lower end of the claimed range is not subject to the rules of rounding and that this court 'has held that there is no need to "read in an implicit range" because an "open-ended range" like "X and up" already expressly represents uncertainty at the top end.'" [Doc. 191 at 7]. The Federal Circuit disagreed, stating: "That other cases have found precision in ranges specific to the claims at issue there, is not of great significance to our analysis here. In other words, there is no blanket rule that ranges, or specifically open-ended ranges, must foreclose rounding. This is especially true in this case where, though not expressly specified, there is in fact an upper limit in the claim because, as a matter of science, pH values are often said to range from 0 to 14." [Id. at 7–8].

Moreover, unlike other claim terms, the disputed claim term lacks approximation language like "about." *See, e.g.*, [Doc. 63-4 at 20:15 ("the bulking agent is present at *about* 1-10%" (emphasis added))]; [Doc. 63-5 at 18:4(ii) ("*about* -30 degrees C. at the rate of *approximately* 0.5 to 0.7 C./min." (emphasis added)].

On appeal, on the one hand, Mylan argued that "a pH of 13" is *exactly* 13 based on the absence of approximation language. On the other hand, Actelion argued that rounding is required because approximation language like "about" signals different variations than those of rounding. Actelion further argued that "it is not practically possible to measure exact pH values" because to get an "exact" measurement "one would have to count every hydrogen ion in solution, which is not scientifically possible."

The Federal Circuit ultimately found that:

> the absence of approximation language [is not] dispositive here. We reject any invitation to create a bright-line rule—either that language like "precisely" or "exactly" is always needed to avoid rounding or that the lack of approximation language, even when it may be found elsewhere in the claims, dictates a precise value. In other words, we find both views equally plausible here; that the absence of approximation language might suggest no approximation, but that the nature of measuring a pH value might nonetheless reasonably require a margin of error.

[Doc. 191 at 8–9]. The Federal Circuit left this Court to answer "[w]hether a pH value can be measured precisely—and to what degree. . . ." [Id. at 9 fn.2]. The Federal Circuit also instructed this Court to "consider whether a pH of 13 carries any meaning to a person of ordinary skill in the art as regards precision of measurement, significant digits, or rounding." [Id.].

2. Specification

The specification is "always highly relevant to the claim construction analysis," and "the single best guide to the meaning of a disputed term." ***Phillips***, 415 F.3d at 1315 (quoting ***Vitronics Corp. v. Conceptronic, Inc.***, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

As the Federal Circuit found and this Court agrees, the specification "reveals that the inventor inconsistently described the level of specificity for a pH of 13" and "supplies the same clarity as to the desired level of precision as muddied water":

> The specification explains that "[t]he pH of the bulk solution is preferably adjusted to about 12.5-13.5, most preferably 13." '802 patent col. 5 ll. 41–43. Mylan argues that this shows that the inventor (1) knew how to use approximation language when it wanted ("about 12.5-13.5") and chose not to for a pH of 13; (2) distinguished a pH value of "12.5" from that of "13"; and (3) distinguished a range ("12.5-13.5") from a definite value ("13"). Appellant's Br. 43–44. In other words, Mylan argues that "13" in "a pH of 13 or higher" cannot be an approximation or range of values, especially a range that encompasses 12.5. Id. Actelion counters, among other things, that "13" should allow rounding or else a preferred embodiment of the invention, meaning a pH of about 12.5 to 13.5, would be excluded from the claim scope. Appellee's Br. 42–43.
>
> There is more. The specification seems to equate a pH of "13.0" to that of "13." Example 4 describes screening several "formulations with the pH of bulk solution . . . adjusted between 10.5 and 13.0." '802 patent col. 10

ll. 63–64. Tables 8 and 9 show the resulting stability data and display a bulk solution pH as "13" with no decimal point. Mylan argues that this shows that the inventor equated a pH of "13" with "13.0." Appellant's Br. 44–45. This may be so. But the specification uses both "13" and "13.0"—and various degrees of precision for pH values generally—throughout. See, e.g., '802 patent col. 7 ll. 16–17 ("The pH of the bulk solution is adjusted to 13.0 with the base."), col. 11 l. 59 ("the pH of bulk solution adjusted to 13"), Tbl. 19 ("pH 11.58"). . . .

This specification stands in sharp contrast to that in ***AstraZeneca***, which helped guide the claim construction at issue there. The issue in ***AstraZeneca*** was whether the concentration of PVP as "0.001%" meant 0.001% within one significant figure—encompassing a concentration of 0.0005% to 0.0014%—or a narrower meaning of precisely 0.001% with even more minor variations. 19 F.4th at 1329. The specification explained that stability was one of the most important factors when determining whether a compound could develop into a therapeutically useful pharmaceutical product. Id. at 1330. It made clear that a formulation comprising 0.001% w/w PVP is more stable than, and different from, a formulation with 0.0005% w/w PVP. Id. at 1332. Indeed, Figure 5 of the patent-at-issue showed that 0.0005% w/w PVP was one of the least stable formulations tested. Id. at 1331–32. Thus, the specification supported a claim construction that would exclude 0.0005% and focus on smaller variations. The data in the specification showed how slight differences in the concentration of PVP,

> down to four decimal places, mattered for stability in the context of that invention. Id. at 1332.
>
> To be sure, the issue here is also stability. But while the specification may state that "the stability of epoprostenol is better at pH 13 compared to lower pH samples," the specification does not evaluate the stability of epoprostenol at pH values between 12 and 13. '802 patent col. 11 ll. 54–56, Tbl. 8. So the specification does not show whether slight differences in the pH, at least between a pH of 12 and 13, matter for stability in the context of this invention. In sum, the scope of the claim term remains unclear even after consulting the specification.

[Doc. 191 at 9–11].

3. Prosecution History

This Court must also read the claims at issue in view of both the written description and prosecution history. ***AstraZeneca AB v. Mylan Pharms. Inc***, 19 F.4th 1325, 1330 (Fed. Cir. 2021). The prosecution history "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." ***Phillips***, 415 F.3d at 1317 (citing ***Vitronics***, 90 F.3d at 1582–53).

As the Federal Circuit noted and this Court agrees, the prosecution history does not provide clarity:

The inventor amended the claim language at issue several times, including: "a pH of greater than 11," J.A. 116; "a pH of greater than 12," J.A. 126; and "a pH of at least 12," J.A. 144. The Examiner rejected the earlier claim language because they found that the prior art "teaches that their composition has a pH of at least 9 and the solutions are capable of being reconstituted to a pH of greater than 12, which encompasses pH of 13 and 14." J.A. 152. In the final rejection, the Examiner explained that the inventor had "not demonstrated that compositions with a pH of greater than 12 are superior to those of [a sample with a pH of 10.5], [but] they have demonstrated that for a pH of 13 there is a significant difference." J.A. 661. The inventor thereafter amended its claim from "a pH of greater than 12" to "a pH of 13 or higher." J.A. 177. The Examiner's reasons for allowance explained that the inventor "has demonstrated unexpected results with respect to compositions made with solutions of pH 13 or higher as shown in tables 8 and 9 of the specification." J.A. 108. Specifically, "stability of the composition is greatly increased when reconstituted versus compositions with a pH of 12 or lower." Id. And that this "is an unexpected result as the prior art does not teach pH of 13 as having advantages over pH 11 or 12." Id.

In short, the prosecution history shows that the Examiner drew a distinction between the stability of a composition with a pH of 13 and that of 12. Such distinction, however, does not illuminate the narrower issue of whether a pH of 13 could encompass values that round to 13, in particular

12.5. Tables 8 and 9 simply do not compare compositions with pH values of 13 to those with a pH between 12 and 13.

[Doc. 191 at 11–12].

B. Extrinsic Evidence

The Federal Circuit found that "this case is one where the proper claim construction cannot be reached without the aid of extrinsic evidence, and that the district court should have considered, at minimum, the textbook excerpts offered and addressed by the parties." [Id. at 12].

The Supreme Court has made clear that there are cases where the district court must "look beyond the patent's intrinsic evidence and . . . consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the relevant art during the relevant time period." ***Teva Pharms. USA, Inc. v. Sandoz, Inc.***, 574 U.S. 318, 331 (2015).

The Federal Circuit has further stated that "[o]nly if a disputed claim term remains ambiguous after analysis of the intrinsic evidence should the court rely on extrinsic evidence." ***Pickholtx v. Rainbow Techs., Inc.***, 284 F.3d 1365, 1372–73 (Fed. Cir. 2002) (citing ***Vitronics***, 90 F.3d at 1583). In these cases, this Court must "make subsidiary factual findings about that extrinsic evidence," and such findings are the evidentiary underpinnings of claim construction. ***Teva***, 574 U.S. at 332.

This Court will first address the three textbooks[2] discussed by the parties on appeal and the Federal Circuit.

pH is a "simple system for communicating concentrations" of hydrogen ions in an aqueous solution. [Doc. 198-1 at 48, 124]. Without the "simple system for communicating concentrations," pH would be a mess of zeros or base-10 exponents. "The concentration of hydronium ions ranges from about 10 mol/L for a concentrated strong acid to about 10^{-15} mol/L for a concentrated strong base. This wide range of concentrations, and the negative powers of 10, are not very convenient to work with." [Id. at 82]. "Expressed as a numerical value without units, the pH of a solution is the negative of the logarithm to the base ten of the hydrogen ion concentration." [Id. at 48]. Below is a chart from Mustoe showing ion concentration values as raw numbers (column 2), exponential notation (column 3), and whole-number pH (column 5), all of them saying the exact same thing:

Table 10.7 *Understanding pH*

Range of acidity and basicity	$[H_3O^+]$ (mol/L)	Exponential notation (mol/L)	log	pH (-log $[H_3O^+]$)
strong acid	1	1×10^{0}	0	0
	0.1	1×10^{-1}	−1	1
	0.01	1×10^{-2}	−2	2
	0.001	1×10^{-3}	−3	3
	0.000 1	1×10^{-4}	−4	4
	0.000 01	1×10^{-5}	−5	5
	0.000 001	1×10^{-6}	−6	6
neutral $[H^+] = [OH^-] = 1.0 \times 10^{-7}$	0.000 000 1	1×10^{-7}	−7	7
	0.000 000 01	1×10^{-8}	−8	8
	0.000 000 001	1×10^{-9}	−9	9
	0.000 000 000 1	1×10^{-10}	−10	10
	0.000 000 000 01	1×10^{-11}	−11	11
	0.000 000 000 001	1×10^{-12}	−12	12
	0.000 000 000 000 1	1×10^{-13}	−13	13
strong base	0.000 000 000 000 01	1×10^{-14}	−14	14

[2] The three textbooks are: Hans van Kessel et al., *Chemistry 12*, Chapter 8.1 (2003) ("Kessel"), Frank Mustoe et al., *Chemistry II*, Chapter 10 (2001) ("Mustoe"), and Martin S. Silberberg, CHEMISTRY: *The Molecular Nature of Matter and Change*, Chapter 18 (4th ed. 2006) ("Silberberg").

[Id. at 387]. As seen above, there is always at least a "1" after the zeros in the raw concentration (column 2), and the base 10 exponent is always accompanied by a "1" figure in exponential notation (column 3). And the "1" is a significant figure. So, for pH "13," all of these expressions are identical:

	0.000 000 000 000 1	1×10^{-13}	−13	13

[Id].

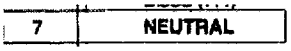
The textbooks explain how to calculate pH and identify significant figures for pH values. Silberberg explains that:

> As with any measurement, the number of significant figures in a pH value reflects the precision with which the concentration is known. However, it is a logarithm, so the number of significant figures in the concentration equals the number of digits *to the right of the decimal point in the logarithm*[.]

[Doc. 198-1 at 124 (emphasis in original)].

Mustoe states: "How do you determine the number of significant digits in a pH? You count only the digits to the right of the decimal point." [Id. at 83]. Kessel echos the same concept, explaining that "the number of digits following the decimal point in the pH value is equal to the number of significant digits in the hydrogen ion concentration," the hydrogen ion concentration being $[H^+_{(aq)}]$. [Id. at 49].

The textbooks of record pervasively use whole-number pH values interchangeably with pH values including one and sometimes two significant figures. Take, for example, the Silberberg textbook when defining a "neutral" pH:



Salt Solution (Examples)	pH
Neutral [NaCl, KBr, $Ba(NO_3)_2$]	7.0

pH of a neutral solution = 7.00
pH of an acidic solution < 7.00
pH of a basic solution > 7.00

[Doc. 198-1 at 775, 797]. Silberberg defines "neutral" pH in three ways: "7," "7.0" and "7.00." Moreover, Kessel equates the terms "pH 3.0," and "pH 3":

Note that the hydrogen ion concentration changes by a multiple of 10 for every increase or decrease of one pH unit. For example, at pH 4.0, $[H^+_{(aq)}]$ is 1×10^{-4} mol/L; at pH 3.0, $[H^+_{(aq)}]$ is 1×10^{-3} mol/L. At pH 3, the $H^+_{(aq)}$ concentration is ten times higher.

[Id. at 49].

The extrinsic evidence further demonstrates that skilled artisans understand at least one significant digit to the right of the decimal place is implied even when discussing ranges of pH value "greater than" or "less than" a certain whole-number pH. Mustoe observes:

$[H_3O^+]$ in neutral water. The pH of the base is 11.00. All basic solutions have a pH that is greater than 7.

[Id. at 83]. On the very next page, Mustoe provides a table showing that a "basic solution" has a pH "greater than 7.00"—so "greater than 7" and "greater than 7.00" are equivalent:

Type of solution	$[H_3O^+]$ (mol/L)	Concentration of hydronium and hydroxide ions	pH at 25°C
acidic solution	greater than 1×10^{-7}	$[H_3O^+] > [OH^-]$	< 7.00
neutral solution	1×10^{-7}	$[H_3O^+] = [OH^-]$	7.00
basic solution	less than 1×10^{-7}	$[H_3O^+] < [OH^-]$	> 7.00

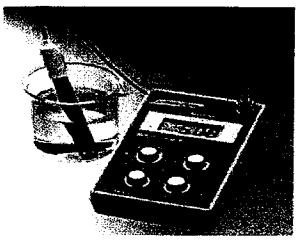
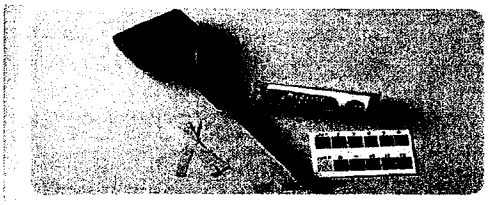
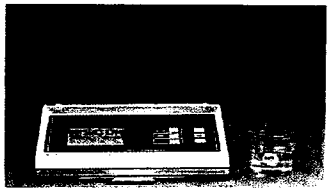
[Id. at 84].

Not only do the textbooks and extrinsic evidence lead this Court to find that pH has two (2) significant digits, but the instrumentation and industry standards for measuring pH related to pharmaceuticals supports this Court's finding.

There are two (2) principal ways to obtain pH values in a laboratory: "an acid-base indicator [i.e., litmus paper] or, more precisely, with an instrument called a pH meter." Acid-base indicators, like litmus paper, "are organic molecules whose colors depend on the acidity or basicity of the solution in which they are dissolved. The pH of a solution is estimated quickly with *pH paper*, a paper strip impregnated with one or a mixture of indicators. A drop of test solution is placed on the paper strip, and the color of the strip is compared with a color chart. . . ." [Id. at 126].

A pH meter "measures [H_3O^+] by means of two electrodes immersed in the test solution. One electrode provides a stable reference voltage; the other has an extremely thin, conducting, glass membrane that separates a known internal [H_3O^+] from the unknown external [H_3O^+]. The differences in [H_3O^+] creates a voltage difference across the membrane, which is measured and displayed in pH units. . . ." [Id.].

pH meters are capable of measuring pH with direct numerical precision—down to at least two decimal places:

[Id. at 52, 87, & 126].

Moreover, the United States Pharmacopeia ("USP"), a well-recognized standard in the pharmaceutical industry would be familiar to a skilled artisan. USP, as of the priority date, explained that: "[f]or compendial purposes, pH is defined as the value given by a suitable, properly standardized, potentiometric instrument (pH meter) capable of reproducing pH values to 0.02 pH unit using an indicator electrode sensitive to hydrogen-ion activity, the glass electrode, and a suitable reference electrode." [Id. at 193].

The U.S. National Institute of Standards and Technology ("NIST") embraces an even narrower margin: "are considered to be accurate to ±0.01 pH unit." [Id. at 216].

The Federal Circuit also noted that "the nature of measuring a pH value might nonetheless reasonably require a margin of error." [Doc. 191 at 9].

With all laboratory instruments, there is some degree of imprecision. The readings of pH levels are no different. For that reason, and as the Federal Circuit hinted at, a margin of error may be needed to account for individual differences in machinery.

In summary, this Court finds based on the conventions conveyed above and in the textbooks, a skilled artisan will understand "a pH of 13 or higher" to refer to a pH value of 13.00. The significant digits for "a pH of 13" is two (2) significant digits. This Court also finds that pH must be measured with a margin of error of, at most, 0.02 pH units on either side. All measurements are important, particularly when it comes to pharmaceuticals. Rounding on any measurement for pharmaceuticals makes this Court uneasy. However, to account for some degree of imprecision, this Court will allow rounding of 0.02 pH units on either side.

V. Conclusion

Applying the above principles and extrinsic evidence to the claim term "a pH of 13 or higher," this Court finds that the skilled artisan would understand the term to have two (2) significant digits and have a lower boundary at a ph of 13.00. The margin of error to account for the accuracy limitations is 0.02 pH units on either side, meaning 12.98 or higher. If this Court were to adopt Actelion's claim construction, that would provide a margin of 0.5 pH on either side—a margin of error 25 times greater than the margin of pH measurement error suggested by USP, and 50 times greater than that adopted by NIST.

The Court **ADOPTS IN PART** Mylan's proposed construction of "a pH of 13 or higher" and **CONSTRUES** it to encompass a margin of error based on the implied significant figure: "a pH of 12.98 or higher."

Lastly, the Motion to Strike Late-Disclosed Declaration of William T. Hensler, Ph.D. (D.I. 198-1) and Request for Leave to Submit Declaration of Christian Schöneich, Ph.D. [Doc. 201], filed December 1, 2023. Therein, Actelion objects to Mylan's untimely submission on November 21, 2023, of the Hensler Declaration, and moves the Declaration be stricken pursuant to Federal Rule of Civil procedure 37(c)(1). The Motion [**Doc. 201**] is **DENIED AS MOOT**. This Court only relied on the extrinsic evidence that the Federal Circuit expressly directed upon remand; this Court did not rely on the Hensler Declaration in formulating this Order.

It is so **ORDERED**.

The Clerk is directed to transmit copies of this Order to any counsel of record herein.

DATED: December 13, 2023.

JOHN PRESTON BAILEY
UNITED STATES DISTRICT JUDGE